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Theoretical study on aquation reaction of *cis*-platin complex: RISM-SCF-SEDD, a hybrid approach of accurate quantum chemical method and statistical mechanics

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The ligand exchange process of *cis*-platin in aqueous solution phase was studied using RISM-SCF-SEDD (reference interaction site model – self-consistent field with spatial electron density distribution) method, a hybrid approach of quantum chemistry and statistical mechanics. The analytical nature of RISM theory enables us to compute accurate reaction free energy in aqueous solution based on CCSD(T), together with microscopic solvation structure around the complex. We found that the solvation effect is indispensable to promote the dissociation of chloride anion from the complex.

1 Introduction

The *cis*-diamminedichloro-platinum (II) (*cis*-platin) is a well-known antitumor drug established in 1970's and still being used.[1,2] The complex is a square planar form due to the d^8 configurations of platinum and only the *cis* isomer exhibits anticancer activity, which is a common feature shared with a numerous derivatives such as carboplatin and spiroplatin.

In the human body, injected *cis*-platin is hydrolyzed to lose a chloride anion.

$$Pt(NH_3)_2Cl_2 + H_2O \rightarrow [Pt(NH_3)_2Cl(H_2O)]^+ + Cl^-. \quad (1)$$

The complex eventually coordinates to the negatively charged DNA to form coordinative bond to nitrogen atoms of nucleobases. X-ray analysis[3] shows that a square-planar platinum center makes bonds with two N7 nitrogens in two guanine bases. The second aquation reaction is considered to occur before the DNA binding,

$$[Pt(NH_3)_2Cl(H_2O)]^+ + H_2O \rightarrow [Pt(NH_3)_2(H_2O)_2]^{2+} + Cl^-, \quad (2)$$

but the experimentally reported rate constant is very slow. In fact, NMR study reported that a large fraction of the complexes exists as the chloroaqua form $[Pt(NH_3)_2Cl(H_2O)]^+$ (**1**).[4,5] Inelastic neutron scattering spectra were reported very recently.[6] It is of great interest how these compounds are hydrated, namely, what is the role of solvent water molecule in the process.

A number of computational studies provided fundamental aspects of this phenomena. The hydrolysis and DNA-biding were studied based on quantum chemical methods such as DFT[7]. It is noted that the consideration of solvation effect is indispensable since the process occurs in cellular condition. In particular, hydrogen bonding is essential to understand the complex-solvent interaction, although dielectric continuum model was adopted in many cases. Monte Carlo simulation provides microscopic solvation structure of surrounding water molecules,[8] but the classical mechanics can not treat bond breaking and formation, which are strongly coupled with solvent effect. Thus only Car-Parrinello type molecular dynamics, QM/MM and their alternative method become a promising approach to address the heart of the reaction.

Carloni et al. reported the interaction of *cis*-platin with water as the first step of the hydrolysis and considered the binding to DNA using Car-Parrinello type simulation.[9] A recent report by Beret et al. discussed the solvation structure in detail.[10] However, there still remain several problems to achieve a comprehensive understanding of the real system. As pointed out by Lopes et al.[8], a number of solvent molecules is necessary to describe the second and further solvation shells. Moreover, it is the free energy change that governs the aquation reaction. An appropriate statistical ensemble is needed to properly evaluate the free energy change along the reaction.

In the present article, we shall report the aquation reaction of *cis*-platin in aqueous solution. To overcome the aforementioned difficulties, accurate free energy change along the

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process was computed using RISM-SCF-SEDD method[11,12]. Reference interaction site model (RISM) utilized in this study is a statistical mechanics theory for molecular liquids[13], and the advantages are summarized as following: (1) The theory provides appropriate statistical ensemble and is free from statistical error, so-called sampling problem. In principle, an infinite number of solvent molecules are dealt with, and 'simulation box' is not required. (2) Since the theory is described in algebraic equation, computational cost is dramatically reduced compared to molecular simulation methods such as molecular dynamics (MD). (3) The inputs of the computation are the same as those of the molecular simulations. The outputs are also basically equivalent to them, but there are several differences. For example, thanks to its analytical nature, solvation free energy ($\Delta\mu_s$) is given by a simple equation as explained below.

RISM-SCF-SEDD method, in which RISM is coupled with molecular orbital theory, is recognized as an alternative to QM/MM. One of big differences is the capability to compute accurate free energy with reasonable computational time due to the advantage of RISM. This allows us to use highly sophisticated electronic structure theory cooperated with solvation effect, and the wave function as well as free energy of the system are readily obtained. The method has been successfully applied to a wide range of chemical phenomenon in solution phase[14] including organometallic reaction[15], chemical reaction in ionic liquid[16], etc. The information of the solvation structure at molecular level provided with RISM-SCF-SEDD method sheds new light on the effect of hydration along this well-known processes.

2 Method

2.1 RISM-SCF-SEDD Theory

It is our intent here to only describe the brief summary of the theory and assume the readers' familiarity of the RISM-SCF family[11,12,17] and statistical mechanics of molecular liquids[13]. More lengthy discussions can be found in the literature and textbooks.[18–20] RISM and closure equations are given as follows.

$$\mathbf{h} = \boldsymbol{\omega}^{\mathrm{U}} * \mathbf{c} * \boldsymbol{\omega}^{\mathrm{V}} + \boldsymbol{\omega}^{\mathrm{U}} * \mathbf{c} * \rho\mathbf{h}^{\mathrm{VV}}, \quad (3)$$

$$h_{\alpha\gamma}(r) = \exp[-\beta u_{\alpha\gamma}(r) + h_{\alpha\gamma}(r) - c_{\alpha\gamma}(r)]. \quad (4)$$

Here $\beta = 1/k_BT$, k_B is Boltzmann constant, the matrix elements of $\boldsymbol{\omega}^{\mathrm{U}}$ and $\boldsymbol{\omega}^{\mathrm{V}}$ are intramolecular correlation function of solute and solvent, respectively. The matrix elements of $\mathbf{h}$ and $\mathbf{c}$ are the total and direct correlation functions between solute and solvent. $\mathbf{h}^{\mathrm{VV}}$ is the total correlation function for solvent with the number density, ρ. Under Gaussian fluctuation approximation,[21] solvation free energy is expressed with the correlation functions as follows;

$$\Delta\mu_s = -\frac{4\pi\rho}{\beta}\sum_{\alpha\gamma}\int_0^\infty (c_{\alpha\gamma} + \frac{1}{2}c_{\alpha\gamma}h_{\alpha\gamma})r^2 dr. \quad (5)$$

In the present approach, solvation effect is taken into account in the Fock operator.

$$F_i = F_i^{\mathrm{gas}} - \sum_j V_j b_j \quad (6)$$

where F_i^{gas} is the Fock operator of an isolated molecule. b_j is the population operator for j-th auxiliary basis sets (ABSs), and V_j is the electrostatic potential on this ABS induced by solvent molecules,

$$V_j = \rho\sum_{\alpha\gamma}\theta_{\alpha j}q_\gamma \int\int \frac{f_j(\mathbf{r}'-\mathbf{r}_\alpha)}{|\mathbf{r}-\mathbf{r}'|}h_{\alpha\gamma}(|\mathbf{r}-\mathbf{r}_\alpha|)d\mathbf{r}d\mathbf{r}', \quad (7)$$

where f_j is auxiliary basis function. $\theta_{\alpha j}$ determines whether j-th ABS is related to the solute site α or not.

$$\theta_{\alpha j} = \begin{cases} 1 & j \in \alpha \\ 0 & j \notin \alpha \end{cases}. \quad (8)$$

The employment of ABS, which has been introduced in RISM-SCF-SEDD,[11] significantly improves the numerical stability of RISM-SCF type calculation. Note that the wave function of the solute (e.g. *cis*-platin) is altered from that in isolated state since the electronic structure of solute and the solvent water distribution around it are determined in a self-consistent manner.

Table 1 Lennard-Jones parameters

	σ/Å	ε/kcal mol^{-1}
Pt[a]	4.780	0.056
Cl[b]	4.200	0.110
N[c]	3.250	0.170
H (NH_3)[c]	1.070	0.055
O[d]	3.166	0.155
H (H_2O)[d]	1.000	0.056

Note that the electronic structure of the solute is determined in a self-consistent manner.
[a] Ref. [15] (a), [b] Ref. [29], [c] Ref. [30], [d] Ref. [17]

3 Computational details

Geometry was optimized in the gas phase using DFT method, where B3LYP functional was employed for the exchange-correlation term.[22,23] Thermal corrections to free energy of translation, rotation, and vibration terms were computed at these geometries. The computations of aqueous solution were carried out using RISM-SCF-SEDD coupled with CCSD(T).

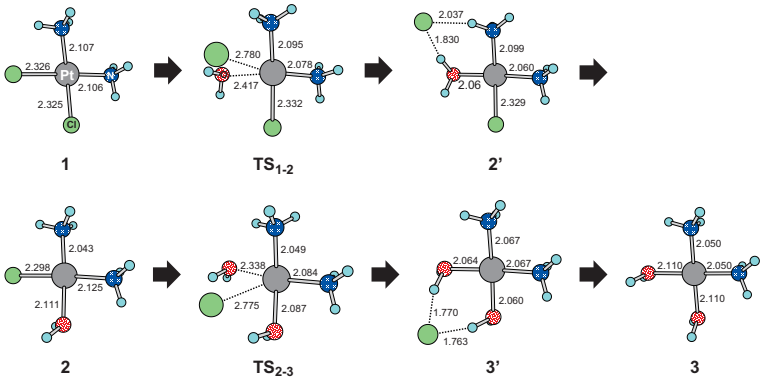

Fig. 1 Geometry changes along hydration reaction of *cis*-platin (unit: angstrom).

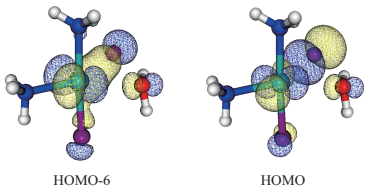

Fig. 2 Kohn-Sham orbitals at $\mathbf{TS}_{1\text{-}2}$

CRENBL basis set was used for Pt[24], cc-pVDZ for hydrogen, carbon, nitrogen, and oxygen atoms[25]. The chloride atom was treated with aug-cc-pVDZ[26].

RISM integral equation was solved with hyper-netted chain (HNC) closure with standard Lennard-Jones parameters taken from the literatures (Table 1). The density of solvent water (ρ) was assumed to be 1.00 g/cm^3. Temperature was taken to be 298.15 K. The optimizations were also performed in aqueous solution for several selected species but the obtained structures closely resemble the gas phase ones: the deviation of bond lengths is less than 0.06 Å. All calculations were performed with GAMESS program package[27]§. RISM-SCF-SEDD module was implemented in the program by us.[11,12] As a standard check of the employed functional, we calculated the energy change in gas phase using another functional, M06. Because the differences in energy obtained with these functionals is less than 0.7kcal/mol (see ESI), we can say that the geometries obtained with B3LYP are reliable.

4 Results and discussion

4.1 Geometry and energy change

cis-platin (**1**) reacts with two water molecules to afford diaqua complex (**3**) as shown in Figure 1. As a water molecule approaches to the *cis*-platin, Pt–Cl bond is lengthened from 2.326 to 2.780 Å at the transition state ($\mathbf{TS}_{1\text{-}2}$), which takes trigonal bipyramidal form. It is interesting that HOMO-6 and HOMO at $\mathbf{TS}_{1\text{-}2}$ respectively show the bonding and antibonding character between Pt d and Cl p orbitals (Figure 2), suggesting that the dissociation of chloride anion is expected to occur readily. But the chloride anion is still attached to the Pt complex due to Coulombic attractive interaction (**2'**), even after Pt–Cl bond breaking is completed.

§ CCSD(T) calculations were performed with CCSD(T) module.[28]

The second aquation step begins from monoaqua complex **2**. Similar to the first ligand exchange process, diaqua complex is formed through the trigonal bipyramidal transition state $\mathbf{TS}_{2\text{-}3}$. The geometrical changes in the both steps resemble each other, in particular the bond lengths of Pt–Cl and Pt–O in $\mathbf{TS}_{2\text{-}3}$ are very close to those in $\mathbf{TS}_{1\text{-}2}$.

The reaction free energy change is shown in Figure 3. In the gas phase, the first aquation takes place with activation barrier of 22.1 kcal/mol. The ligand exchange may be completed to give the complex, **2'**, but it is infeasible to take a step further because of extremely high energy to reach **2** (108.2 kcal/mol). It means that even if **2'** is formed, the backward reaction should occur. The dissociation of chloride anion to form **2** requires large amounts of energy to overcome the strong attraction between Pt complex and anion. The same goes for the second aquation step. Activation barrier (25.9 kcal/mol) from **2** to **3'** is similar to the first aquation, and further 195.7 kcal/mol is necessary to complete the exchange reaction to afford **3**. The situation is, however, drastically changed in aqueous solution. At the first aquation (**1**→**2'**), the reaction free energy in aqueous phase is not so different from the gas phase one. It is noted that the barrier to the first aquation is about 23 kcal/mol, which is very close to the experimental value (24 kcal/mol[31]). The result indicates that the exchange reaction occurs under a mild condition. In the next step, chloride anion is dissociated from monoaqua complex. Although this step requires large energy in the gas phase, generated charged products, **2** and $\mathbf{Cl}^-$, are independently solvated and strongly stabilized in aqueous solution. Namely, the stabilization due to solvation effect significantly stimulates the dissociation of chloride anion. This feature is commonly found in dissociative ionic species in solution phase. The strong attractive interaction between two charged species is screened by polar solvent, and the dissociative path becomes preferable. The same argument is applicable to the final step. The chloride anion readily dissociates from **3'** in aqueous solution to afford diaqua com-

Table 2 Gross Mulliken charges in aqueous solution q_{aq} and their difference from the gas phase values Δq ($|e|$).

	q_{aq}							$\Delta q = q_{aq} - q_{gas}$						
	Pt	Cl[a]	Cl[b]	NH_3[c]	NH_3[d]	H_2O[a]	H_2O[b]	Pt	Cl[a]	Cl[b]	NH_3[c]	NH_3[d]	H_2O[a]	H_2O[b]
1	0.92	-0.76	-0.76	0.30	0.30	0.00	0.00	0.02	-0.10	-0.10	0.09	0.09	0.00	0.00
TS$_{1\text{-}2}$	0.96	-0.96	-0.79	0.31	0.32	0.15	0.00	-0.04	-0.08	-0.07	0.08	0.09	0.01	0.00
2'	0.92	-0.95	-0.77	0.30	0.32	0.19	0.00	-0.03	-0.07	-0.07	0.06	0.09	0.01	0.00
2	0.92	-1.00	-0.75	0.28	0.34	0.20	0.00	-0.01	0.00	-0.11	0.06	0.04	0.02	0.00
TS$_{2\text{-}3}$	0.97	-1.00	-0.95	0.31	0.31	0.20	0.16	-0.03	0.00	-0.09	0.04	0.05	0.01	0.01
3'	0.93	-1.00	-0.87	0.30	0.30	0.17	0.17	-0.01	0.00	-0.09	0.04	0.04	0.01	0.01
3	0.99	-1.00	-1.00	0.32	0.32	0.18	0.18	-0.01	0.00	0.00	0.00	0.00	0.00	0.00

[a]Replaced in the first exchange reaction (**1**⇌**2**). [b]Replaced in the second exchange reaction (**2**⇌**3**).
[c]*cis* position to the first leaving chloride ligand. [d]*trans* position to the first leaving chloride ligand.

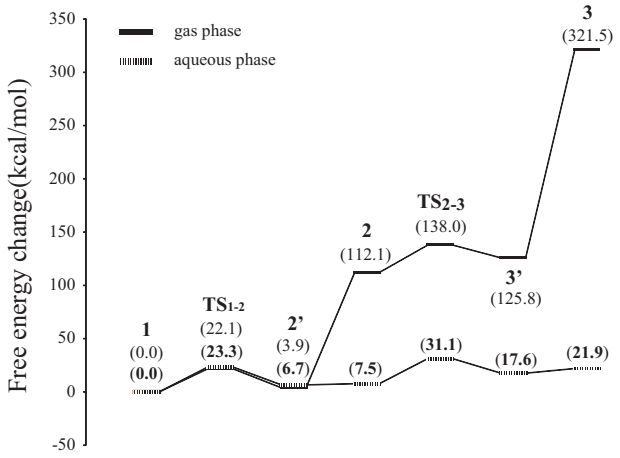

Fig. 3 Free energy changes of the reaction in the gas phase, and in aqueous phase

plex **3**.

The experimentally determined equilibrium constants of **1** ⇌ **2** (pK_1) and **2** ⇌ **3** (pK_2) by Hindmarsh et al.[34] are respectively 2.07 and 3.49. Davies et al. also reported 2.17 and 3.53[4]. Using the computed free energy difference in pure water shown in Figure 3, the corresponding values are estimated to be 3.74 and 8.81. The tendency, in which the second step is more difficult to occur, is correctly predicted in the preset treatment. Although the system considered here is different from the *in vitro* experimental condition, the computational results reasonably agree with the experiments. A more highly sophisticated treatment may be necessary to perfectly coincide with the experimental values. But more importantly, the energy profile in aqueous solution is drastically changed from that in the gas phase. If the gas-phase free energy difference is applied, the evaluated pK_1 and pK_2 differ by more than two orders of magnitude. We would like to emphasize that solvation effect is indispensable to understand the process even in the qualitative sense, and the satisfactory agreement with experimental results was obtained by the present treatment. It is also noted that, the concentration of chloride anion ($pCl = -\log[Cl^-]$) under physiological conditions is considerably different from *in vitro* environment. In fact, pCl is usually considered about 2.4[35] in cell, and pCl ∼ 0.99 in the blood.

4.2 Electronic structure

Hydration effect generally enhances the polarization among atoms in a molecule. In Table 2, Mulliken charges in aqueous solution (q_{aq}), and their differences from the gas phase values (Δq) are listed. Because of the negative charge of chloride and the positive charge of amine group, **1** has large dipole moment even in the gas phase (12.2D). The polarization is further enhanced in aqueous phase (16.2D). As shown in the table, NH_3 groups and Pt atom donate electrons to Cl atom, and the charges around NH_3 groups become more positive, while those around Cl atoms become more negative. The polarization due to the solvation effect becomes less prominent as the reaction proceeds. The population assigned to NH_3 and H_2O ligand groups of **3** in aqueous solution are virtually the same as those in the gas phase. In general, the electronic structure of cationic species is less polarizable with respect to the electric field generated by surrounding solvent molecules compared to neutral and anionic species. The great stabilization in **2** and **3** is attributed to simple Coulombic interaction between the charged species and solvent water molecules since the contribution from the polarization is not so significant. It is interesting to note that the charge assigned on Pt is not significantly changed during the reaction. The charge alteration is less pronounced in aqueous solution, especially on the two transition states.

4.3 Hydration in aqueous phase

In RISM and RISM-SCF theory, solvation structure is described in a set of radial distribution functions (RDFs). Fig.4 displays RDFs between solvent water oxygen and hydrogen atoms in a water molecule replacing chloride ligand in the

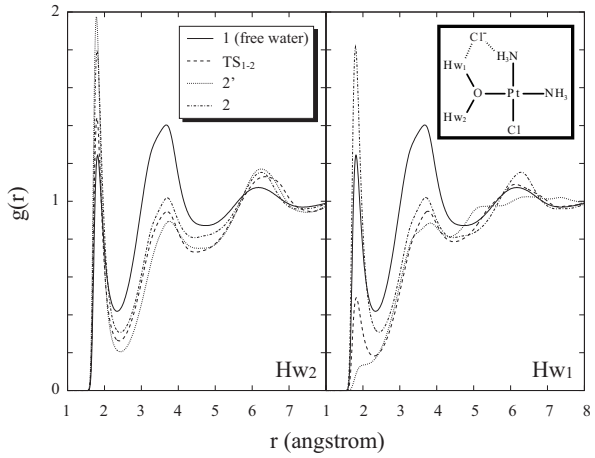

Fig. 4 RDFs between solvent-water oxygen and the hydrogens in the replacing aquo ligand (Hw_1 and Hw_2).

complex. At the first, the water is a free molecule. The equivalent two hydrogen atoms (Hw_1 and Hw_2) show a typical hydrogen-bonding RDFs around 2.0Å. On the first exchange step, Hw_1 is closer to the leaving chloride anion being highly negatively charged (Table 2). This minus charge prevents solvent-water oxygen from approaching to Hw_1, and remarkably lowers the height of the RDF at **2'**, which is displayed schematically in the right upper panel in the figure. After the dissociation, the height of RDF between Hw_1 and solvent oxygen is again increased to become higher than the peak of free water molecule. On the other hand, Hw_2 is always exposed to solvent and the peak becomes higher as increasing the assigned charge from 0.21 in **1** to 0.27 in **2**. The solvation structure change in the second step (**2**→**3**) is very similar to the first step.

One may think that the solvation structure around Pt is drastically changed along the reaction. However, the RDF remains almost unchanged through the reaction (see ESI†). A slight increasing of the height is observed in the chloride RDFs but the alteration is not significant. This is consistent with the fact that the charge assigned to the metal is not changed along the reaction as listed in table 2. As indicated above, the leaving chloride anion is strongly hydrated as the reaction proceeds. The peak height of RDF with water oxygen becomes gradually higher (see ESI†). This hydration of chloride anion is a driving force of the process, and significantly contributes to the remarkable stabilization of the product. The free energy difference between the gas and aqueous phases shown in Fig. 3 is mainly attributed to the generation of these charged species.

5 Conclusions

We studied the aquo-exchange reaction of *cis*-platin complex in aqueous phase using RISM-SCF-SEDD method. This method is an alternative to QM/MM technique but enables us to perform highly accurate quantum chemical method with modest computational demands. The present result clearly demonstrates that the energy profile is drastically affected by the solvation, and the reaction occurs only in aqueous environment. Moreover, a set of radial distribution functions gives us useful information on the solvation structure at molecular level. The computationally obtained free energy change along the reaction is consistent with experimental results, and the monoaquo complex could be a dominant species in a realistic condition of the chloride concentration.

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Appendix

Within the framework of hybrid computational methods such as RISM-SCF-SEDD and PCM, the reaction free energy ($\Delta_r G^0$) in pure water is computed by

$$\Delta_r G^0 = \Delta_r G_g^{\ominus} + \Delta G_s, \tag{9}$$

where $\Delta_r G_g^{\ominus}$ is the reaction Gibbs free energy at standard state in gas phase, which is the sum of the electronic, translation, rotation, and vibration contributions. ΔG_s is the sum of the free energy change of solvation related to Eq. 5 and the electronic reorganization (polarization) energy. The equilibrium constant is directly computed by the standard relationship.

For the acid dissociation in the presence of an excess of water molecules, experimentally obtained acid dissociation constant (K_a) in aqueous solution is given by

$$pK_a = \frac{\Delta_r G_a^0}{2.303RT} - \log c_w, \tag{10}$$

where c_w is the molar concentrations of H_2O. This is the standard procedure to evaluate the reaction free energy in aqueous solution, and applied to the present work as well as to numerous studies[40].

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